



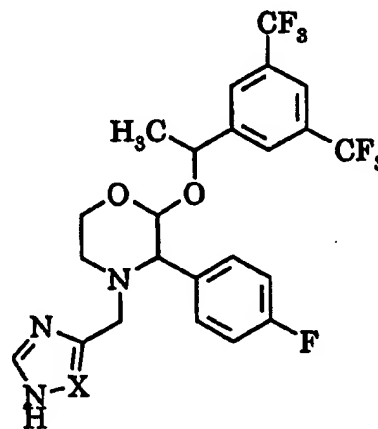
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 413/06, A61K 31/535	A1	(11) International Publication Number: WO 95/30674 (43) International Publication Date: 16 November 1995 (16.11.95)
<p>(21) International Application Number: PCT/GB95/00983</p> <p>(22) International Filing Date: 1 May 1995 (01.05.95)</p> <p>(30) Priority Data: 9408960.4 5 May 1994 (05.05.94) GB 9408963.8 5 May 1994 (05.05.94) GB</p> <p>(71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): HAWORTH, Karen, Elizabeth [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). TEALL, Martin, Richard [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). SEWARD, Eileen, Mary [IE/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). SWAIN, Christopher, John [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).</p> <p>(74) Agent: HISCOCK, Ian, James; Merck & Co., Inc., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).</p>	<p>(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	

(54) Title: MORPHOLINE DERIVATIVES AND THEIR USE AS ANTAGONISTS OF TACHIKININS

(57) Abstract

The present invention relates to compounds of formula (I): wherein X is N or CH; and pharmaceutically acceptable salts and prodrugs thereof. The compounds are of particular use in the treatment of pain, inflammation, migraine and emesis.



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MORPHOLINE DERIVATIVES AND THEIR USE AS ANTAGONISTS OF TACHYKININS

This invention relates to novel compounds which are useful
5 as tachykinin antagonists, particularly as antagonists of substance P.
More particularly, the invention relates to morpholine derivatives,
processes for their preparation, pharmaceutical compositions containing
them, and their use in medicine.

The tachykinins are a group of naturally occurring peptides
10 found widely distributed throughout mammalian tissues, both within the
central nervous system and in peripheral nervous and circulatory
systems.

The tachykinins are distinguished by a conserved carboxyl-
terminal sequence:
15 Phe-X-Gly-Leu-Met-NH₂.

At present, there are three known mammalian tachykinins
referred to as substance P, neurokinin A (NKA, substance K, neuromedin
L) and neurokinin B (NKB, neuromedin K) (for review see J.E. Maggio,
Peptides (1985) 6(suppl. 3), 237-242). The current nomenclature
20 designates the three tachykinin receptors mediating the biological actions
of substance P, NKA and NKB as the NK₁, NK₂ and NK₃ receptors,
respectively.

Evidence for the usefulness of tachykinin receptor
antagonists in pain, headache, especially migraine, Alzheimer's disease,
25 multiple sclerosis, attenuation of morphine withdrawal, cardiovascular
changes, oedema, such as oedema caused by thermal injury, chronic
inflammatory diseases such as rheumatoid arthritis, asthma/bronchial
hyperreactivity and other respiratory diseases including allergic rhinitis,
inflammatory diseases of the gut including ulcerative colitis and Crohn's
30 disease, ocular injury and ocular inflammatory diseases, proliferative
vitreoretinopathy, irritable bowel syndrome and disorders of bladder

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function including cystitis and bladder detruser hyper-reflexia is reviewed in "Tachykinin Receptors and Tachykinin Receptor Antagonists", C.A. Maggi, R. Patacchini, P. Rovero and A. Giachetti, *J. Auton. Pharmacol.* (1993) 13, 23-93.

5 For instance, substance P is believed *inter alia* to be involved in the neurotransmission of pain sensations [Otsuka *et al*, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 Substance P in the Nervous System, *Ciba Foundation Symposium* 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, 10 "Does Substance P Act as a Pain Transmitter?" *TIPS* (1987) 8, 506-510], specifically in the transmission of pain in migraine (B.E.B. Sandberg *et al*, *J. Med Chem*, (1982) 25, 1009) and in arthritis [Levine *et al* in *Science* (1984) 226, 547-549]. Tachykinins have also been implicated in 15 gastrointestinal (GI) disorders and diseases of the GI tract such as inflammatory bowel disease [Mantyh *et al* in *Neuroscience* (1988) 25(3), 817-37 and D. Regoli in "Trends in Cluster Headache" Ed. Sicuteri *et al* Elsevier Scientific Publishers, Amsterdam (1987) page 85)] and emesis [F. D. Tattersall *et al*, *Eur. J. Pharmacol.*, (1993) 250, R5-R6]. It is also 20 hypothesised that there is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd *et al* "A Neurogenic Mechanism for Symmetrical Arthritis" in *The Lancet*, 11 November 1989 and Grönblad *et al*, "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in *J. Rheumatol.* (1988) 15(12), 1807-10]. Therefore, substance P is believed to be involved in the inflammatory response in 25 diseases such as rheumatoid arthritis and osteoarthritis, and fibrositis [O'Byrne *et al*, *Arthritis and Rheumatism* (1990) 33, 1023-8]. Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet *et al*, *Can. J. Pharmacol. Physiol.* (1988) 66, 1361-7], immunoregulation [Lotz *et al*, *Science* (1988) 241, 1218-21 and 30 Kimball *et al*, *J. Immunol.* (1988) 141(10), 3564-9] vasodilation,

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bronchospasm, reflex or neuronal control of the viscera [Mantyh *et al*,
Proc. Natl. Acad. Sci., USA (1988) 85, 3235-9] and, possibly by arresting
or slowing β -amyloid-mediated neurodegenerative changes [Yankner *et al*,
Science (1990) 250, 279-82] in senile dementia of the Alzheimer type,
5 Alzheimer's disease and Down's Syndrome.

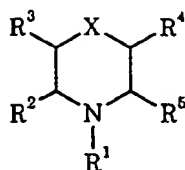
Tachykinin antagonists may also be useful in the treatment
of small cell carcinomas, in particular small cell lung cancer (SCLC)
[Langdon *et al*, *Cancer Research* (1992) 52, 4554-7].

Substance P may also play a role in demyelinating diseases
10 such as multiple sclerosis and amyotrophic lateral sclerosis [J. Luber-
Narod *et al*, poster *C.I.N.P. XVIIIth Congress*, 28th June-2nd July 1992],
and in disorders of bladder function such as bladder detrusor hyper-
reflexia (*The Lancet*, 16th May 1992, 1239).

It has furthermore been suggested that tachykinins have
15 utility in the following disorders: depression, dysthymic disorders, chronic
obstructive airways disease, hypersensitivity disorders such as poison ivy,
vasospastic diseases such as angina and Reynauld's disease, fibrosing and
collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex
sympathetic dystrophy such as shoulder/hand syndrome, addiction
20 disorders such as alcoholism, stress related somatic disorders, neuropathy,
neuralgia, disorders related to immune enhancement or suppression such
as systemic lupus erythmatosus (European patent specification no.
0 436 334), ophthalmic disease such as conjunctivitis, vernal conjunctivitis,
and the like, and cutaneous diseases such as contact dermatitis, atopic
25 dermatitis, urticaria, and other eczematoïd dermatitis (European patent
specification no. 0 394 989).

European patent specification no. 0 577 394 (published 5th
January 1994) discloses morpholine and thiomorpholine tachykinin
receptor antagonists of the general formula

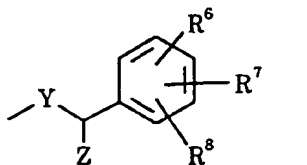
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wherein R¹ is a large variety of substituents;

R² and R³ are *inter alia* hydrogen;

5 R⁴ is *inter alia*



R⁵ is *inter alia* optionally substituted phenyl;

10 R⁶, R⁷ and R⁸ are a variety of substituents;

X is O, S, SO or SO₂;

Y is *inter alia* O; and

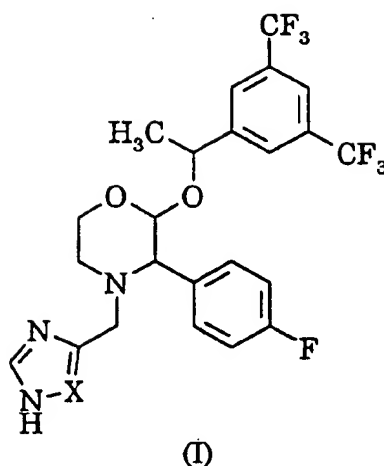
Z is hydrogen or C₁₋₄ alkyl.

We have found the compounds of the present invention to be
 15 particularly potent and useful antagonists of tachykinins, especially of
 substance P.

It is desirable that compounds may be administered orally
 and by injection. Certain compounds have now been discovered which act
 as potent non-peptide tachykinin antagonists and which, by virtue of their
 20 advantageous aqueous solubility, are particularly easily formulated for
 administration by both the oral and injection routes, for example, in
 aqueous media.

The present invention provides compounds which have the
 formula (I):

- 5 -



where X is N or CH;

and pharmaceutically acceptable salts and prodrugs thereof.

5 For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention

10 include acid addition salts which may, for example, be formed by mixing a solution of a compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Salts of amine groups may

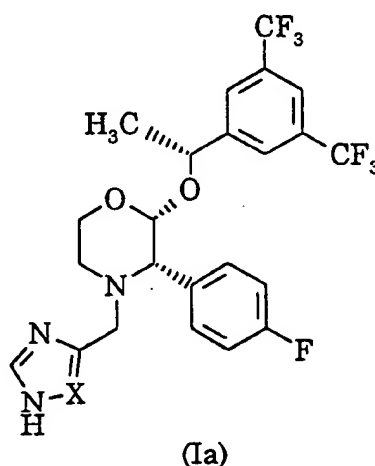
15 also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety.

The compounds according to the invention have three asymmetric centres, and may accordingly exist both as enantiomers and

20 as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

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The preferred compounds of formula (I) will have the 2- and 3- substituent cis and the preferred stereochemistry at the 2-position is that possessed by the compounds of Examples 1 and 2 (i.e. 2-(R)-), the preferred stereochemistry of the 3-position is that possessed by the compounds of Examples 1 and 2 (i.e. 3-(S)), and the stereochemistry of the carbon to which the α -methyl group is attached is preferably (R), i.e. compounds of the formula (Ia):



10

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible *in vivo* into the required compounds of formula (I).

15 Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of

20

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some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality.

Thus, for example, certain preferred prodrugs may not be antagonists of tachykinin, particularly substance P, activity to any significant extent (or not at all). Such compounds, however, are still advantageous in treating the various conditions described herein, especially where an injectable formulation is preferred.

The advantages of a prodrug may lie in its physical properties, such as enhanced water solubility for parenteral administration compared with the parent drug, or it may enhance absorption from the digestive tract, or it may enhance drug stability for long-term storage. Ideally a prodrug will improve the overall efficacy of a parent drug, for example, through the reduction of toxicity and unwanted effects of drugs by controlling their absorption, blood levels, metabolism, distribution and cellular uptake.

It will be appreciated that in the compounds of formula (I) above, the 1,2,4-triazol-3-yl or 1,3-imidazol-4-yl group may be derivatized to give a prodrug of the compounds of the present invention.

Suitable prodrug derivatives include:

- (a) $-(\text{CHR}^{10})_n-\text{PO}(\text{OH})\text{O}^-\cdot\text{M}^+$;
- (b) $-(\text{CHR}^{10})_n-\text{PO}(\text{O}^-)_2\cdot 2\text{M}^+$;
- (c) $-(\text{CHR}^{10})_n-\text{PO}(\text{O}^-)_2\cdot\text{D}^{2+}$;
- (d) $-(\text{CHR}^{10})_n-\text{SO}_3^-\cdot\text{M}^+$;
- (e) $-\text{COCH}_2\text{CH}_2\text{CO}_2^-\cdot\text{M}^+$;
- (f) $-\text{COH}$;
- (g) $-\text{CO}(\text{CH}_2)_n\text{N}(\text{R}^{10})_2$; and
- (h) $-(\text{CH}(\text{R}^{10})\text{O})_n-\text{COR}^{11}$,

wherein

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n is zero or 1;

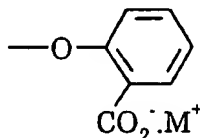
M⁺ is a pharmaceutically acceptable monovalent counterion;

D²⁺ is a pharmaceutically acceptable divalent counterion;

R¹⁰ is hydrogen or C_{1,3}alkyl; and

- 5 R¹¹ is a group selected from -O(CH₂)₂NH₃⁺.M⁻;
 -O(CH₂)₂NH₂(R¹²)⁺.M⁻; -OCH₂CO₂⁻.M⁺;
 -OCH(CO₂⁻.M⁺)CH₂CO₂⁻.M⁺; -OCH₂CH(NH₃⁺)CO₂⁻;
 -OC(CO₂⁻.M⁺)(CH₂CO₂⁻.M⁺)₂; and

10



in which M⁻ is a pharmaceutically acceptable monovalent counterion, and
 R¹² is hydrogen, C_{1,4}alkyl or C_{2,4}alkyl substituted by a hydroxyl or
 C_{1,4}alkoxy group.

15

Particularly preferred prodrug derivatives are:

- (a) -(CHR¹⁰)_n-PO(OH)O⁻.M⁺;
 (b) -(CHR¹⁰)_n-PO(O⁻)₂.2M⁺;
 (c) -(CHR¹⁰)_n-PO(O⁻)₂.D²⁺;

20

especially where n is zero.

- The term "parent molecule", "parent compound" or "parent
 drug" refers to the biologically active entity that is released via enzymatic
 action of a metabolic or catabolic process, or via a chemical process
 25 following administration of the prodrug. The parent compound may also
 be the starting material for the preparation of its corresponding prodrug.

While all of the usual routes of administration are useful
 with the above prodrugs, the preferred routes of administration are oral
 and intravenous. After gastrointestinal absorption or intravenous

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administration, the prodrugs are hydrolyzed or otherwise cleaved *in vivo* to the corresponding parent compound of formula (I), or a pharmaceutically acceptable salt thereof.

Examples of negative monovalent counterions defined herein as "M⁻" include acetate, adipate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, citrate, ethanesulfonate, fumarate, hemisulfate, 2-hydroxyethylsulfonate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactate, malate, maleate, methanesulfonate, 2-naphthalenesulfonate, oxalate, pamoate, persulfate, picrate, pivalate, propionate, salicylate, stearate, succinate, sulfate, tartrate, tosylate (p-toluenesulfonate), and undecanoate.

Base salts (which are pharmaceutically acceptable monovalent cations defined herein as "M⁺" or pharmaceutically acceptable divalent cations defined herein as "D²⁺", if appropriate) include ammonium salts, alkali metal salts such as sodium, lithium and potassium salts, alkaline earth metal salts such as aluminium, calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, ornithine, and so forth. If M⁺ is a monovalent cation, it is recognised that if the definition 2M⁺ is present, each of M⁺ may be the same or different. In addition, it is similarly recognised that if the definition 2M⁺ is present, a divalent cation D²⁺ may instead be present. Also, the basic nitrogen-containing groups may be quaternized with such agents as: lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl and dibutyl; diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; aralkyl halides like benzyl bromide and others. The non-toxic physiologically acceptable salts are preferred, although other salts are also useful, such as in isolating or purifying the product.

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The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze
5 drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

The present invention further provides pharmaceutical
10 compositions comprising a compound of formula (I) in association with a pharmaceutically acceptable carrier or excipient.

Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal
15 administration, or administration by inhalation or insufflation.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or
20 gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is
25 dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention.
30 The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of

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prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

10 The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and
15 similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

 Preferred compositions for administration by injection
20 include those comprising a compound of formula (I), as the active ingredient, in association with a surface-active agent (or wetting agent or surfactant) or in the form of an emulsion (as a water-in-oil or oil-in-water emulsion).

 Suitable surface-active agents include, in particular, non-
25 ionic agents, such as polyoxyethylenesorbitans (e.g. Tween™ 20, 40, 60, 80 or 85) and other sorbitans (e.g. Span™ 20, 40, 60, 80 or 85). Compositions with a surface-active agent will conveniently comprise between 0.05 and 5% surface-active agent, and preferably between 0.1 and 2.5%. It will be appreciated that other ingredients may be added, for example mannitol or
30 other pharmaceutically acceptable vehicles, if necessary.

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Suitable emulsions may be prepared using commercially available fat emulsions, such as Intralipid™, Liposyn™, Infontrol™, Lipofundin™ and Lipiphysan™. The active ingredient may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (e.g. soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g. egg phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example glycerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion will preferably comprise fat droplets between 0.1 and 1.0µm, particularly 0.1 and 0.5µm, and have a pH in the range of 5.5 to 8.0.

Particularly preferred emulsion compositions are those prepared by mixing a compound of formula (I) with Intralipid™ or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The present invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of

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formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as dementia, including AIDS related dementia, senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and other neuropathological disorders such as peripheral neuropathy, for example AIDS related neuropathy, diabetic and chemotherapy-induced neuropathy, and postherpetic and other neuralgias; neuronal damage, such as cerebral ischemic damage and cerebral edema in cerebrovascular disorders; small cell carcinomas such as small cell lung cancer; respiratory diseases, particularly those associated with excess mucus secretion such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, asthma, and bronchospasm; airways diseases modulated by neurogenic inflammation; diseases characterised by neurogenic mucus secretion, such as cystic fibrosis; diseases associated with decreased glandular secretions, including lacrimation, such as Sjogren's syndrome, hyperlipoproteinemias IV and V, hemochromatosis, sarcoidosis, and amyloidosis; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, ocular inflammation, osteoarthritis, rheumatoid arthritis, pruritis and sunburn; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, dry eye syndrome, and the like; ophthalmic conditions associated with cell proliferation such as proliferative vitreoretinopathy; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis;

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addiction disorders including the withdrawal response produced by chronic treatment with, or abuse of, drugs such as benzodiazepines, opiates, cocaine, alcohol and nicotine; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera, ulcerative colitis, Crohn's disease, irritable bowel syndrome and emesis, including acute, delayed, post-operative, late phase or anticipatory emesis such as emesis induced by chemotherapy, radiation, toxins, viral or bacterial infections, pregnancy, vestibular disorders, motion, surgery, migraine, opioid analgesics, and variations in intercranial pressure, in particular, for example, drug or radiation induced emesis or post-operative nausea and vomiting; disorders of bladder function such as cystitis, bladder detrusor hyper-reflexia and incontinence; fibrosing and collagen diseases such as scleroderma and eosinophilic fasciitis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

Hence, the compounds of the present invention may be of use in the treatment of physiological disorders associated with excessive stimulation of tachykinin receptors, especially neurokinin-1 receptors, and as neurokinin-1 antagonists for the control and/or treatment of any of the aforementioned clinical conditions in mammals, including humans.

The compounds of formula (I) are also of value in the treatment of a combination of the above conditions, in particular in the treatment of combined post-operative pain and post-operative nausea and vomiting.

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The compounds of formula (I) are particularly useful in the treatment of emesis, including acute, delayed, post-operative, late phase or anticipatory emesis, such as emesis or nausea induced by chemotherapy, radiation, toxins, such as metabolic or microbial toxins, viral or bacterial infections, pregnancy, vestibular disorders, motion, mechanical stimulation, gastrointestinal obstruction, reduced gastrointestinal motility, visceral pain, psychological stress or disturbance, high altitude, weightlessness, opioid analgesics, intoxication, resulting for example from consumption of alcohol, surgery, migraine, and variations in intercranial pressure. Most especially, the compounds of formula (I) are of use in the treatment of emesis induced by antineoplastic (cytotoxic) agents including those routinely used in cancer chemotherapy.

Examples of such chemotherapeutic agents include alkylating agents, for example, nitrogen mustards, ethyleneimine compounds, alkyl sulphonates and other compounds with an alkylating action such as nitrosoureas, cisplatin and dacarbazine; antimetabolites, for example, folic acid, purine or pyrimidine antagonists; mitotic inhibitors, for example, vinca alkaloids and derivatives of podophyllotoxin; and cytotoxic antibiotics.

Particular examples of chemotherapeutic agents are described, for instance, by D. J. Stewart in *"Nausea and Vomiting: Recent Research and Clinical Advances"*, Eds. J. Kuucharczyk *et al*, CRC Press Inc., Boca Raton, Florida, USA (1991) pages 177-203, especially page 188. Commonly used chemotherapeutic agents include cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin and chlorambucil [R. J. Gralla *et al* in *Cancer Treatment Reports* (1984) 68(1), 163-172].

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The compounds of formula (I) are also of use in the treatment of emesis induced by radiation including radiation therapy such as in the treatment of cancer, or radiation sickness; and in the treatment of post-operative nausea and vomiting.

5 It will be appreciated that the compounds of formula (I) may be presented together with another therapeutic agent as a combined preparation for simultaneous, separate or sequential use for the relief of emesis. Such combined preparations may be, for example, in the form of a twin pack.

10 A further aspect of the present invention comprises the compounds of formula (I) in combination with a 5-HT₃ antagonist, such as ondansetron, granisetron or tropisetron, or other anti-emetic medicaments, for example, a dopamine antagonist such as metoclopramide or GABA_B receptor agonists such as baclofen.

15 Additionally, a compound of formula (I) may be administered in combination with an anti-inflammatory corticosteroid, such as dexamethasone, triamcinolone, triamcinolone acetonide, flunisolide, budesonide, or others such as those disclosed in US patent nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and

20 3,749,712. Dexamethasone (Decadron™) is particularly preferred. Furthermore, a compound of formula (I) may be administered in combination with a chemotherapeutic agent such as an alkylating agent, antimetabolite, mitotic inhibitor or cytotoxic antibiotic, as described above. In general, the currently available dosage forms of the known therapeutic

25 agents for use in such combinations will be suitable.

When tested in the ferret model of cisplatin-induced emesis described by F. D. Tattersall *et al*, in *Eur. J. pharmacol.*, (1993) 250, R5-R6, the compounds of the present invention were found to attenuate the retching and vomiting induced by cisplatin.

30 The compounds of formula (I) are also particularly useful in the treatment of pain or nociception and/or inflammation and disorders

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associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis, headache and especially migraine.

5 The present invention further provides a compound of formula (I) for use in therapy.

 According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated
10 with an excess of tachykinins, especially substance P.

 The present invention also provides a method for the the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing
15 amount of a compound of formula (I) or a composition comprising a compound of formula (I).

 For the treatment of certain conditions it may be desirable to employ a compound according to the present invention in conjunction with another pharmacologically active agent. For example, for the treatment of
20 respiratory diseases such as asthma, a compound of formula (I) may be used in conjunction with a bronchodilator, such as a β_2 -adrenergic receptor antagonist or tachykinin antagonist which acts at NK-2 receptors. The compound of formula (I) and the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

25 Likewise, a compound of the present invention may be employed with a leukotriene antagonists, such as a leukotriene D₄ antagonist such as a compound selected from those disclosed in European patent specification nos. 0 480 717 and 0 604 114 and in US patent nos. 4,859,692 and 5,270,324. This combination is particularly useful in the
30 treatment of respiratory diseases such as asthma, chronic bronchitis and cough.

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The present invention accordingly provides a method for the treatment of a respiratory disease, such as asthma, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) and an effective amount of a
5 bronchodilator.

The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

It will be appreciated that for the treatment or prevention of
10 migraine, a compound of the present invention may be used in conjunction with other anti-migraine agents, such as ergotamines or 5-HT₁ agonists, especially sumatriptan.

Likewise, for the treatment of behavioural hyperalgesia, a compound of the present invention may be used in conjunction with an
15 antagonist of N-methyl D-aspartate (NMDA), such as dizocilpine.

For the treatment or prevention of inflammatory conditions in the lower urinary tract, especially cystitis, a compound of the present invention may be used in conjunction with an antiinflammatory agent such as a bradykinin receptor antagonist.

20 In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day.

For example, in the treatment of conditions involving the
25 neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compound may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

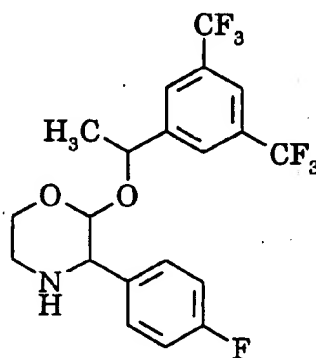
30 In the treatment of emesis using an injectable formulation, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about

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0.005 to 5 mg/kg per day, and especially 0.01 to 1 mg/kg per day. The compound may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

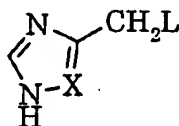
It will be appreciated that the amount of the compound of formula (I) required for use in any treatment will vary not only with the particular composition selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

According to a process (A), the compounds of the present invention may be prepared from the compound of formula (II)



(II)

by reaction with a compound of formula (III):



(III)

or a protected derivative thereof, wherein X is N or CH, and L is a leaving group such as a halogen atom, for example, chlorine, bromine or iodine or

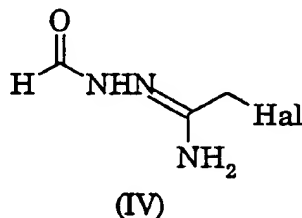
- 20 -

an alkyl- or arylsulphonyloxy group, for example, a mesylate or tosylate group, followed where necessary by deprotection in a conventional manner.

One particularly suitable protecting group for the compounds of formula (III) is the p-toluenesulphonyl group.

This reaction may be performed in conventional manner, for example in an organic solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate.

Alternatively, according to a process (B), the compound of formula (I) in which X is N may be prepared by reaction of an intermediate of formula (II) with a compound of formula (IV)



wherein Hal is a halogen atom, for example, bromine, chlorine or iodine, in the presence of a base.

Suitable bases of use in the reaction include alkali metal carbonates such as, for example, potassium carbonate. The reaction is conveniently effected in an anhydrous organic solvent such as, for example, anhydrous dimethylformamide, preferably at elevated temperature, such as between 60°C and 140°C.

Further details of suitable procedures will be found in the accompanying Examples.

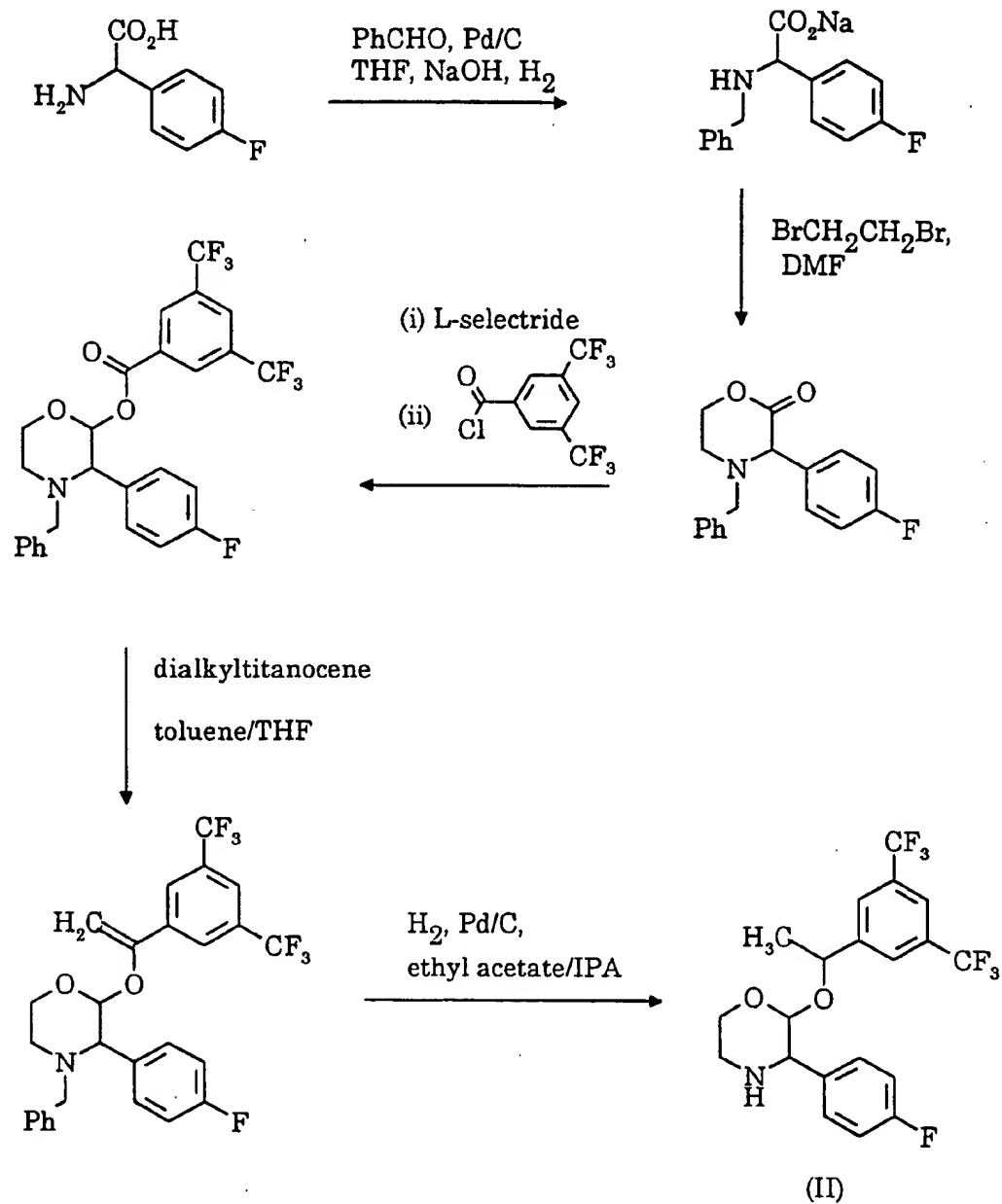
Compounds of formula (III) are commercially available or may be prepared by the procedures described in the accompanying Examples or from commercially available compounds by methods readily apparent to one skilled in the art.

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Compounds of formula (IV) may be prepared as described in *J. Med. Chem.*, 27, 849 (1984).

The compounds of the formula (II) may be prepared as shown in the following Scheme:

5



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The following references describe methods which may be applied by the skilled worker to the chemical synthesis set forth above once the skilled worker has read the disclosure herein.

- (i) D.A. Evans *et al.*, *J. Am. Chem. Soc.*, 112, 4011 (1990).
- 5 (ii) Yanagisawa, I. *et al.*, *J. Med. Chem.*, 27, 849 (1984).
- (iii) Duschinsky, R. *et al.*, *J. Am. Chem. Soc.*, 70, 657 (1948).
- (iv) Tebbe F. N. *et al.*, *J. Am. Chem. Soc.*, 100, 3611 (1978).
- (v) Petasis, N. A. *et al.*, *J. Am. Chem. Soc.*, 112, 6532 (1990).
- (vi) Takai, K. *et al.*, *J. Org. Chem.*, 52, 4412 (1987).

10 The Examples disclosed herein produce predominantly the preferred isomers. The unfavoured isomers are also produced as minor components. If desired they may be isolated and employed to prepare the various stereoisomers in conventional manner, for example chromatography using an appropriate chiral column. However, the
15 skilled worker will appreciate that although the Examples have been optimized to the production of the preferred isomers, variation in solvent, reagents, chromatography etc can be readily employed to yield the other isomers.

L-Selectride is lithium tri-sec-butylborohydride.

20 During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and
25 P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The compounds of the present invention were tested by the methods set out at pages 36 to 39 of International Patent Specification No.
30 WO 93/01165. The compounds were both found to be active with IC₅₀ at the NK1 receptor of 0.1nM.

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DESCRIPTION 1(S)-(4-Fluorophenyl)glycineVia Chiral Synthesis:Step A: 3-(4-Fluorophenyl)acetyl-4-(S)-benzyl-2-oxazolidinone

5 An oven-dried, 1 L 3-necked flask, equipped with a septum, nitrogen inlet, thermometer, and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 5.09g (33.0mmol) of 4-fluorophenylacetic acid in 100ml of anhydrous ether. The solution was cooled to -10°C and treated with 5.60ml (40.0mmol) of triethylamine
10 followed by 4.30ml (35.0mmol) of trimethylacetyl chloride. A white precipitate formed immediately. The resulting mixture was stirred at -10°C for 40 minutes, then cooled to -78°C.

 An oven-dried, 250ml round bottom flask, equipped with a septum
15 and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 5.31g (30.0mmol) of 4-(S)-benzyl-2-oxazolidinone in 40ml of dry THF. The solution was stirred in a dry ice/acetone bath for 10 minutes, then 18.8ml of 1.6M n-butyllithium solution in hexanes was slowly added. After 10 minutes, the lithiated oxazolidinone solution was
20 added, via cannula, to the above mixture in the 3-necked flask. The cooling bath was removed from the resulting mixture and the temperature was allowed to rise to 0°C. The reaction was quenched with 100ml of saturated aqueous ammonium chloride solution, transferred to a 1l flask, and the ether and THF were removed *in vacuo*. The concentrated mixture
25 was partitioned between 300ml of methylene chloride and 50ml of water and the layers were separated. The organic layer was washed with 100ml of 2N aqueous hydrochloric acid solution, 300ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate and concentrated *in vacuo*. Flash chromatography on 400g of silica gel using
30 3:2 v/v hexanes/ether as the eluant afforded 8.95g of an oil that slowly

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solidified on standing. Recrystallisation from 10:1 hexanes/ether afforded 7.89g (83%) of the title compound as a white solid: mp 64-66°C. MS (FAB): m/z 314 ($M^+ + H$, 100%), 177 ($M - ArCH_2CO + H$, 85%). 1H NMR (400MHz, $CDCl_3$) δ 2.76 (1H, dd, $J=13.2, 9.2$ Hz), 3.26 (dd, $J=13.2, 3.2$ Hz),
5 4.16-4.34 (4H, m), 4.65 (1H, m), 7.02-7.33 (9H, m).

Analysis Calcd. for $C_{18}H_{16}FNO_3$: C, 69.00; H, 5.15; N, 4.47; F, 6.06;
Found: C, 68.86; H, 5.14; N, 4.48; F, 6.08%

Step B: 3-((S)-Azido-(4-fluorophenyl))acetyl-4-(S)-benzyl-2-oxazolidinone

- 10 An oven-dried, 1l 3-necked flask, equipped with a septum, nitrogen inlet, thermometer, and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 58.0ml of 1M potassium bis(trimethylsilyl)amide solution in toluene and 85ml of THF and was cooled to -78°C. An oven-dried 250ml round-bottomed flask, equipped
15 with a septum and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 7.20g (23.0mmol) of 3-(4-fluorophenyl)acetyl-4-(S)-benzyl-2-oxazolidinone (from Step A) in 40ml of THF. The acyl oxazolidinone solution was stirred in a dry ice/acetone bath for 10 minutes, then transferred, via cannula, to the potassium
20 bis(trimethylsilyl)amide solution at such a rate that the internal temperature of the mixture was maintained below -70°C. The acyl oxazolidinone flask was rinsed with 15ml of THF and the rinse was added, via cannula, to the reaction mixture and the resulting mixture was stirred at -78°C for 30 minutes. An oven-dried, 250ml round-bottomed flask,
25 equipped with a septum and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 10.89g (35.0mmol) of 2,4,6-triisopropylphenylsulfonyl azide in 40ml of THF. The azide solution was stirred in a dry ice/acetone bath for 10 minutes, then transferred, via cannula, to the reaction mixture at such a rate that the internal
30 temperature of the mixture was maintained below -70°C. After 2 minutes, the reaction was quenched with 6.0ml of glacial acetic acid, the cooling

- 25 -

bath was removed and the mixture was stirred at room temperature for 18 hours. The quenched reaction mixture was partitioned between 300ml of ethyl acetate and 300ml of 50% saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried over magnesium sulfate, and concentrated *in vacuo*. Flash chromatography on 500g of silica gel using 2:1 v/v, then 1:1 v/v hexanes/methylene chloride as the eluant afforded 5.45g (67%) of the title compound as an oil. IR Spectrum (neat, cm^{-1}): 2104, 1781, 1702. ^1H NMR (400MHz, CDCl_3) δ 2.86 (1H, dd, $J=13.2$, 9.6Hz), 3.40 (1H, dd, $J=13.2$, 3.2Hz), 4.09-4.19 (2H, m), 4.62-4.68 (1H, m), 6.14 (1H, s), 7.07-7.47 (9H, m).

Analysis Calcd. for $\text{C}_{18}\text{H}_{15}\text{FN}_4\text{O}_3$: C 61.01; H, 4.27; N, 15.81; F, 5.36;

Found: C, 60.99; H, 4.19; N, 15.80; F, 5.34%

Step C: (S)-Azido-(4-fluorophenyl)acetic acid

A solution of 5.40g (15.2mmol) of 3-((S)-azido-(4-fluorophenyl)) acetyl-4-(S)-benzyl-2-oxazolidinone (from Step B) in 200ml of 3:1 v/v THF/water was stirred in an ice bath for 10 minutes. 1.28g (30.4mmol) of lithium hydroxide monohydrate was added in one portion and the resulting mixture was stirred cold for 30 minutes. The reaction mixture was partitioned between 100ml of methylene chloride and 100ml of 25% saturated aqueous sodium bicarbonate solution and the layers were separated. The aqueous layer was washed with 2 x 100ml of methylene chloride and acidified to pH 2 with 2N aqueous hydrochloric acid solution. The resulting mixture was extracted with 2 x 100ml of ethyl acetate; the extracts were combined, washed with 50ml of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated *in vacuo* to afford 2.30g (77%) of the title compound as an oil that was used in the following step without further purification. IR Spectrum (neat, cm^{-1}): 2111, 1724. ^1H NMR (400MHz, CDCl_3) δ 5.06 (1H, s), 7.08-7.45 (4H, m), 8.75 (1H, br s).

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Step D: (S)-(4-Fluorophenyl)glycine

A mixture of 2.30g (11.8mmol) of (S)-azido-(4-fluorophenyl)acetic acid (from Step C), 2.50mg 10% palladium on carbon catalyst and 160ml 3:1 v/v water/acetic acid was stirred under an atmosphere of hydrogen for 18 hours. The reaction mixture was filtered through Celite and the flask and filter cake were rinsed well with ~1l of 3:1 v/v water/acetic acid. The filtrate was concentrated *in vacuo* to about 50ml of volume. 300ml of toluene was added and the mixture concentrated to afford a solid. The solid was suspended in 1:1 v/v methanol/ether, filtered and dried to afford 1.99g (100%) of the title compound. ¹H NMR (400MHz, D₂O+ NaOD) δ 3.97 (1H, s), 6.77 (2H, app t, J=8.8Hz), 7.01 (2H, app t, J=5.6Hz).

Via Resolution:15 Step A' (4-Fluorophenyl)acetyl chloride

A solution of 150g (0.974mol) of 4-(fluorophenyl)acetic acid and 1ml of N,N-dimethylformamide in 500ml of toluene at 40°C was treated with 20ml of thionyl chloride and heated to 40°C. An additional 61.2ml of thionyl chloride was added dropwise over 1.5 hours. After the addition, the solution was heated at 50°C for 1 hour, the solvent was removed *in vacuo* and the residual oil was distilled at reduced pressure (1.5mmHg) to afford 150.4g (89.5%) of the title compound, bp = 68-70°C.

Step B': Methyl 2-bromo-3-(4-fluorophenyl)acetate

25 A mixture of 150.4g (0.872mol) of 4-(fluorophenyl)acetyl chloride (from Step A') and 174.5g (1.09mol) of bromine was irradiated at 40-50°C with a quartz lamp for 5 hours. The reaction mixture was added dropwise to 400ml of methanol and the solution was stirred for 16 hours. The solvent was removed *in vacuo* and the residual oil was distilled at reduced pressure (1.5mmHg) to afford 198.5g (92%) of the title compound, bp = 106-110°C.

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Step C': Methyl (±)-(4-fluorophenyl)glycine

A solution of 24.7g (0.1mol) of methyl 2-bromo-2-(4-fluorophenyl) acetate (from Step B') and 2.28g (0.01mol) of benzyl triethylammonium chloride in 25ml of methanol was treated with 6.8g (0.105mol) of sodium azide and the resulting mixture was stirred for 20 hours at room temperature. The reaction mixture was filtered; the filtrate was diluted with 50ml of methanol and hydrogenated in the presence of 0.5g of 10% Pd/C at 50 psi for 1 hour. The solution was filtered and the solvent removed *in vacuo*. The residue was partitioned between 10% aqueous sodium carbonate solution and ethyl acetate. The organic phase was washed with water, saturated aqueous sodium chloride solution dried over magnesium sulfate and concentrated *in vacuo* to afford 9.8g of the title compound as an oil.

Step D': Methyl (S)-(4-fluorophenyl)glycinate

A solution of 58.4g of methyl (±) 4-(fluorophenyl)glycinate (from Step C') in 110ml of 7:1 v/v ethanol/water was mixed with a solution of 28.6g (0.0799mol) of O,O'-(+)-dibenzoyltartaric acid ((+)-DBT) (28.6g, 0.0799mol) in 110ml of 7:1 v/v ethanol:water and the resulting solution was allowed to age at room temperature. Ethyl acetate (220ml) was added after crystallisation was complete and the resulting mixture was cooled to -20°C and filtered to afford 32.4g of methyl (S)-(4-fluorophenyl)glycinate, (+)-DBT salt (ee = 93.2%). The mother liquors were concentrated *in vacuo* and the free base was liberated by partitioning between ethyl acetate and aqueous sodium carbonate solution. A solution of free base, so obtained, in 110ml of 7:1 v/v ethanol/water was mixed with a solution of 28.6g (0.0799mol) of O,O'-(-)-dibenzoyltartaric acid ((-)-DBT) (28.6g, 0.0799mol) in 110ml of 7:1 v/v ethanol:water and the resulting solution was allowed to age at room temperature. Ethyl acetate (220ml) was added after crystallisation was complete and the resulting mixture was cooled to -20°C

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and filtered to afford 47.0g of methyl (R)-(4-fluorophenyl)glycinate, (-)-DBT salt (ee = 75.8%). Recycling of the mother liquors and addition of (+)-DBT gave a second crop of 7.4g of (S)-(4-fluorophenyl)glycinate, (+)-DBT salt (ee = 96.4%). The two crops of the (S)-amino ester (39.8g) were combined in 200ml of 7:1 v/v ethanol/water, heated for 30 minutes and cooled to room temperature. Addition of ethyl acetate, cooling, and filtration afforded 31.7g of (S)-(4-fluorophenyl)glycinate, (+)-DBT salt (ee > 98%). Enantiomeric excess was determined by chiral HPLC (Crownpak CR(+) 5% MeOH in aq HClO₄ pH2 1.5ml/min 40°C 200nm).

10

A mixture of 17.5g of (S)-(4-fluorophenyl)glycinate, (+)-DBT salt and 32ml of 5.5N HCl (32ml) was heated at reflux for 1.5 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in 40ml of water. The aqueous solution was washed (3 x 30ml of ethyl acetate) and the layers were separated. The pH of the aqueous layer was adjusted to 7 using ammonium hydroxide and the precipitated solid was filtered to afford 7.4g of the title compound (ee = 98.8%).

15

DESCRIPTION 2

20

4-Benzyl-3-(S)-(4-fluorophenyl)-2-morpholinone

Step A: N-Benzyl-(S)-(4-fluorophenyl)glycine

A solution of 1.87g (11.05mmol) of (S)-(4-fluorophenyl)-glycine (from Description 1) and 1.12ml (11.1mmol) of benzaldehyde in 11.1ml of 1N aqueous sodium hydroxide solution and 11ml of methanol at 0°C was treated with 165mg (4.4mmol) of sodium borohydride. The cooling bath was removed and the resulting mixture was stirred at room temperature for 30 minutes. Second portions of benzaldehyde (1.12ml (11.1mmol)) and sodium borohydride (165mg (4.4mmol)) were added to the reaction mixture and stirring was continued for 1.5hours. The reaction mixture was

25

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- 29 -

partitioned between 100ml of ether and 50ml of water and the layers were separated. The aqueous layer was separated and filtered to remove a small amount of insoluble material. The filtrate was acidified to pH 5 with 2N aqueous hydrochloric acid solution and the solid that had

5 precipitated was filtered, rinsed well with water, then ether, and dried to afford 1.95g of the title compound. ¹H NMR (400MHz, D₂O + NaOD) δ 3.33 (2H, AB q, J=8.4Hz), 3.85 (1H, s), 6.79-7.16 (4H, m).

Step B: 4-Benzyl-3-(S)-(4-fluorophenyl)-2-morpholinone

10 A mixture of 1.95g (7.5mmol) of N-benzyl (S)-(4-fluorophenyl) glycine, 3.90ml (22.5mmol) of N,N-diisopropyl-ethylamine, 6.50ml (75.0mmol) of 1,2-dibromoethane and 40ml of N,N-dimethylformamide was stirred at 100°C for 20 hours (dissolution of all solids occurred on warming). The reaction mixture was cooled and concentrated *in vacuo*.

15 The residue was partitioned between 250ml of ether and 100ml of 0.5N potassium hydrogen sulfate solution and the layers were separated. The organic layer was washed with 100ml of saturated aqueous sodium bicarbonate solution, 3 x 150ml of water, dried over magnesium sulfate, and concentrated *in vacuo*. Flash chromatography on 125g of silica gel

20 using 3:1 v/v hexanes/ether as the eluant afforded 1.58g (74%) of the title compound as an oil. ¹H NMR (400MHz, CDCl₃) δ 2.65 (1H, dt, J=3.2, 12.8Hz), 3.00 (1H, dt, J=12.8, 2.8Hz), 3.16 (1H, d, J=13.6Hz), 3.76 (1H, d, J=13.6Hz), 4.24 (1H, s), 4.37 (1H, dt, J=13.2, 3.2Hz), 4.54 (1H, dt, J=2.8, 13.2Hz), 7.07-7.56 (9H, m).

25

DESCRIPTION 3

4-Benzyl-2-(R)-(3,5-bis(trifluoromethyl)benzoyloxy)-3-(S)-(4-fluorophenyl) morpholine

30 A solution of 2.67g (10.0mmol) of 4-benzyl-3-(S)-(4-fluorophenyl)-2-morpholinone (Description 2) in 40ml of dry THF was cooled to -78°C. The

- 30 -

cold solution was treated with 12.5ml of 1.0M L-Selectride® solution in THF, maintaining the internal reaction temperature below -70°C. The resulting solution was stirred cold for 45 minutes and the reaction was charged with 3.60ml(20.0mmol) of 3,5-bis(trifluoromethyl)benzoyl chloride. The resulting yellow mixture was stirred cold for 30 minutes and the reaction was quenched with 50ml of saturated aqueous sodium bicarbonate solution. The quenched mixture was partitioned between 300ml of ether and 50ml of water and the layers were separated. The organic layer was dried over magnesium sulfate. The aqueous layer was extracted with 300ml of ether; the extract was dried and combined with the original organic layer. The combined organics were concentrated *in vacuo*. Flash chromatography on 150g of silica gel using 37:3 v/v hexanes/ether as the eluant afforded 4.06g (80%) of the title compound as a solid. ¹H NMR (200MHz, CDCl₃) δ 2.50 (1H, dt, J=3.4, 12.0Hz), 2.97 (1H, app d, J=12.0Hz), 2.99 (1H, d, J=13.6Hz), 3.72-3.79 (1H, m), 3.82 (1H, d, J=2.6Hz), 4.00 (1H, d, J=13.6Hz), 4.20 (dt, J=2.4, 11.6Hz), 6.22 (1H, d, J=2.6Hz), 7.22-7.37 (7H, m), 7.57 (2H, app d, J=6.8Hz), 8.07 (1H, s), 8.47 (2H, s). MS (FAB) m/z 528 (M+H, 25%), 270 (100%).

Analysis Calcd. for C₂₆H₂₀F₇NO₃: C, 59.21; H, 3.82; N, 2.66; F, 25.21.

Found: C, 59.06; H, 4.05; N, 2.50; F, 25.18%

DESCRIPTION 4

4-Benzyl-2-(R)-(1-(3,5-bis(trifluoromethyl)phenyl)ethenyloxy)-3-(S)-(4-fluorophenyl)morpholine

Step A: Dimethyl titanocene

A solution of 2.49g (10.0mmol) of titanocene dichloride in 50ml of ether in the dark at 0°C was treated with 17.5ml of 1.4M methyllithium solution in ether maintaining the internal temperature below 5°C. The resulting yellow/orange mixture was stirred at room temperature for 30

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minutes and the reaction was quenched by slowly adding 25g of ice. The quenched reaction mixture was diluted with 50ml of ether and 25ml of water and the layers were separated. The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to afford 2.03g (98%) of the title compound as a light-sensitive solid. The dimethyl titanocene could be stored as a solution in toluene at 0°C for at least 2 weeks without apparent chemical degradation. ¹H NMR (200MHz, CDCl₃) δ -0.15 (6H, s), 6.06 (10H, s).

10 Step B: 4-Benzyl-2-(R)-(1-(3,5-bis(trifluoromethyl)phenyl)ethenyloxy)-3-(S)-(4-fluorophenyl)morpholine

A solution of the compound of Description 3 (2.50g, 4.9mmol) and 2.50g (12.0mmol) of dimethyl titanocene (from Step A) in 35ml of 11 v/v THF/toluene was stirred in an oil bath at 80°C for 16 hours. The reaction mixture was cooled and concentrated *in vacuo*. Flash chromatography on 150g of silica gel using 3:1 v/v hexanes/methylene chloride as the eluant afforded 1.71g (69%) of the title compound as a solid. An analytical sample was obtained via recrystallisation from isopropanol: ¹H NMR (400MHz, CDCl₃) δ 2.42 (1H, dt, J=3.6, 12.0Hz), 2.90 (1H, app d, J=12.0Hz), 2.91 (1H, d, J=13.6Hz), 3.62-3.66 (1H, m), 3.72 (1H, d, J=2.6Hz), 3.94 (1H, d, J=13.6Hz), 4.09 (1H, dt, J=2.4, 12.0Hz), 4.75 (1H, d, J=3.2Hz), 4.82 (1H, d, J=3.2Hz), 5.32 (1H, d, J=2.6Hz), 7.09 (2H, t, J=8.8Hz), 7.24-7.33 (5H, m), 7.58-7.62 (2H, m), 7.80 (1H, s), 7.90 (2H, s); MS (FAB) 526 (M+H, 75%), 270 (100%).

25 Analysis Calcd. for C₂₇H₂₂F₇NO₂: C, 61.72; H, 4.22; N, 2.67; F, 25.31.
Found: C, 61.79; H, 4.10; N, 2.65; F, 25.27%

DESCRIPTION 5

30 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine

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The compound of Description 4 (4.0g) was dissolved in ethyl acetate (50ml) and isopropanol (16ml). To this solution was added palladium on charcoal (1.5g) and the mixture was hydrogenated at 40 psi for 36h. The catalyst was removed by filtration through Celite and the solvents were removed *in vacuo*. The residue was purified by flash chromatography on silica using 100% ethyl acetate and then 1-10% methanol in ethyl acetate. This afforded isomer A 500mg (15%) and isomer B 2.6g (80%) as clear oils - isomer B crystallised on standing. For the title compound: ¹H NMR (400MHz, CDCl₃) δ 1.16 (3H, d, J=6.8Hz), 1.80 (1H, br s), 3.13 (1H, dd, J=3.2, 12.4Hz), 3.23 (1H, dt, J=3.6, 12.4Hz), 3.63 (1H, dd, J=2.4, 11.2Hz), 4.01 (1H, d, J=2.4Hz), 4.13 (1H, dt, J=3.2, 12.0Hz), 4.42 (1H, d, J=2.4Hz), 4.19 (1H, q, J=6.8Hz), 7.04-7.09 (2H, m), 7.27-7.40 (4H, m), 7.73 (1H, s); MS (FAB) 438 (M+H, 75%), 180 (100%).

15

EXAMPLE 1

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine

A solution of the compound of Description 5 (3.77g) and potassium carbonate (3.59g) in dry dimethylformamide (7ml) was stirred at room temperature for 10 min. N-Formyl-2-chloroacetamidrazone (prepared according to Yanagisawa I., *J. Med Chem.* 1984, 27, 849) was added and the reaction mixture was heated at 60°C for 1 hour. The temperature was then increased to 140°C for 2h. The mixture was cooled and partitioned between ethyl acetate and water and the organic phase was washed with water, brine, dried (MgSO₄) and evaporated to give a brown oil. The residue was purified by chromatography on silica using 1-5% methanol in dichloromethane. This afforded the product as a white foam (2.99g). ¹H NMR (360MHz, DMSO) δ 8.25 (1H, s), 7.85 (1H, s), 7.50 (2H, t), 7.37 (2H, s), 7.11 (2H, t, J=9.0Hz), 4.93 (1H, q, J=6.6Hz), 4.32 (1H, d, J=2.8Hz), 4.09

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(1H, dt, J=11.5Hz), 3.63 (1H, d, J=14.1Hz), 3.59 (1H, d, J=3.0Hz), 3.17 (1H, d, J=14.0Hz), 2.49 (1H, dt, J=15.7Hz), 1.36 (3H, d, J=6.6Hz). MS (CI⁺) m/z 519.

Analysis Calcd. for C₂₃H₁₉F₇N₄O₂: C, 53.29; H, 4.08; N, 10.81;

5 Found: C, 52.92; H, 3.94; N, 10.33%

EXAMPLE 2

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(1,3-imidazol-4-yl)methylmorpholine

10 Step A: 4-Hydroxymethyl-N-(p-toluenesulfonyl)imidazole

4-Hydroxymethylimidazole hydrochloride (10g) was suspended in dichloromethane (200ml). p-Toluenesulfonyl chloride (15.58g) was added and triethylamine (25.8ml) was added dropwise to the stirred reaction mixture which was allowed to stir at room temperature overnight. The
15 mixture was washed with water (2 x 100ml) and brine (1 x 100ml) and the organic layer was dried and evaporated to leave a clear oil which was recrystallised from ethyl acetate/hexane to afford a white crystalline solid (15g, 80%). ¹H NMR (360MHz, CDCl₃) δ 2.44 (3H, s), 4.55 (2H, s), 7.21 (1H, s), 7.35 (2H, d, J=8.0Hz), 7.62 (2H, d, J=8.0Hz), 7.98 (1H, s). MS
20 (CI⁺) m/z 253 (M+H, 100%).

Step B: ((N-p-Toluenesulfonyl)imidazol-2-yl)methyl methanesulfonate

The alcohol described in (a) above (1g) was dissolved in dichloromethane (15ml) and the solution was cooled in an ice-methanol
25 bath. Triethylamine (0.4g) was added dropwise in dichloromethane (1ml) followed by methanesulfonyl chloride (0.45g). The mixture was washed with water (2 x 10ml) and brine (1 x 10ml) and the organic layer was dried and evaporated to leave a white crystalline powder (1.3g). This was used in the next reaction without further purification. ¹H NMR (360MHz,
30 CDCl₃) δ 2.45 (3H, s), 3.00 (3H, s), 5.13 (2H, s), 7.39 (2H, d, J=8.0Hz),

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7.40 (1H, s), 7.84 (2H, d, J=8.0Hz), 8.00 (1H, s). MS (CI⁺) m/z 267 ((M-CH₃O)⁺, 30%).

5 Step C: 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(N-p-toluenesulfonyl-1,3-imidazol-4-yl)methylmorpholine

The compound of Description 5 (500mg), potassium carbonate (474mg) and the mesylate referred to in (b) above (432mg) were suspended in N,N-dimethylformamide (5ml) and the resulting mixture was stirred at 60°C for 4hr. The mixture was cooled and diluted with water (50ml). The mixture was extracted with ethyl acetate (3 x 20ml) and the organic layer was washed with brine, dried (MgSO₄) and evaporated. The residue was purified by column chromatography on silica using 30% ethyl acetate in petrol as eluant to afford the product (515mg, 70%) as a white crystalline solid. MS (CI⁺) m/z 672 ((M+H)⁺, 100%).

15

Step D: 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(1,3-imidazol-4-yl)methylmorpholine

The compound referred to in (c) above (500mg) was deprotected by treatment with ethereal hydrogen chloride. The mixture was evaporated *in vacuo* and the residue was triturated with ether several times and the ethereal washings were decanted to remove the liberated p-toluenesulfonyl chloride. The residual product was treated with aqueous potassium carbonate to liberate the free base and this was extracted with ethyl acetate. The organic layer was washed with water, brine, dried (MgSO₄) and evaporated *in vacuo*. The residue was purified by column chromatography on silica using 2-6% methanol in dichloromethane as eluant. ¹H NMR (250MHz, CDCl₃) δ 1.45 (3H, d, J=7.0Hz), 2.55 (1H, dt, J=12.0, 3.0Hz), 2.96 (1H, d, J=12.0Hz), 3.18 (1H, d, J=14.0Hz), 3.41 (1H, d, J=3.0Hz), 3.67 (1H, m), 3.71 (1H, d, J=14.0Hz), 4.25 (1H, m), 4.31 (1H, d, J=3.0Hz), 4.86 (1H, q, J=7.0Hz), 6.81 (1H, s),

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7.05 (2H, t, J=8.0Hz), 7.13 (2H, s), 7.42 (2H, br s), 7.63 (1H, s), 7.68 (1H, s). MS (CI⁺) m/z 518 ((M+H)⁺, 20%).

- 5 The following examples illustrate pharmaceutical compositions according to the invention.

EXAMPLE 3A Tablets containing 1-25mg of compound

		<u>Amount mg</u>		
10	Compound of formula (I)	1.0	2.0	25.0
	Microcrystalline cellulose	20.0	20.0	20.0
	Modified food corn starch	20.0	20.0	20.0
	Lactose	58.5	57.5	34.5
	Magnesium Stearate	0.5	0.5	0.5

15

EXAMPLE 3B Tablets containing 26-100mg of compound

		<u>Amount mg</u>		
	Compound of formula (I)	26.0	50.0	100.0
	Microcrystalline cellulose	80.0	80.0	80.0
20	Modified food corn starch	80.0	80.0	80.0
	Lactose	213.5	189.5	139.5
	Magnesium Stearate	0.5	0.5	0.5

- 25 The compound of formula (I), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet.

30

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EXAMPLE 4 Parenteral injection

	<u>Amount mg</u>
Compound of formula (I)	1 to 100mg
Citric Acid Monohydrate	0.75mg
5 Sodium Phosphate	4.5mg
Sodium Chloride	9mg
Water for injection	to 10ml

- 10 The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The compound of formula (I) is dissolved or suspended in the solution and made up to volume.

EXAMPLE 5 Topical formulation

	<u>Amount mg</u>
15 Compound of formula (I)	1-10g
Emulsifying Wax	30g
Liquid paraffin	20g
White Soft Paraffin	to 100g

- 20 The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The compound of formula (I) is added and stirring continued until dispersed. The mixture is then cooled until solid.

25 Example 6A - (Surface-Active Agent) Injection Formulation

Compound of formula (I)	up to 10mg/kg
Tween 80™	up to 2.5%
[in 5% aqueous mannitol (isotonic)]	

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The compound of formula (I) is dissolved directly in a solution of the commercially available Tween 80™ (polyoxyethylenesorbitan monooleate) and 5% aqueous mannitol (isotonic).

5 Example 6B - (Emulsion) Injection Formulation

Compound of formula (I) up to 30mg/ml
Intralipid™ (10-20%)

10 The compound of formula (I) is dissolved directly in the commercially available Intralipid™ (10 or 20%) to form an emulsion.

Example 6C - Alternative (Emulsion) Injectable Formulation

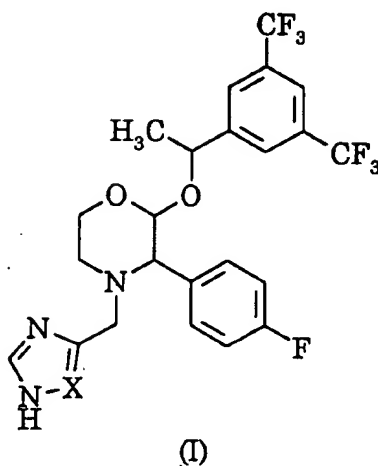
	<u>Amount</u>
Compound of formula (I)	0.1 - 10mg
15 Soybean oil	100mg
Egg phospholipid	6mg
Glycerol	22mg
Water for injection	to 1ml

20 All materials are sterilized and pyrogen free. The compound of formula (I) is dissolved in soybean oil. An emulsion is then formed by mixing this solution with the egg phospholipid, glycerol and water. The emulsion is then sealed in sterile vials.

CLAIMS

1. A compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof:

5



wherein X is N or CH.

10

2. The compound:

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine;
or a pharmaceutically acceptable salt or prodrug thereof.

15

3. The compound:

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(1,3-imidazol-4-yl)methylmorpholine;
or a pharmaceutically acceptable salt or prodrug thereof.

20

4. A compound as claimed in any one of claims 1 to 3 for use in therapy.

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5. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to 3 in association with a pharmaceutically acceptable carrier or excipient.

5 6. A method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound according to Claim 1, or a pharmaceutically acceptable salt or prodrug thereof, or a composition
10 comprising a compound according to Claim 1, or a pharmaceutically acceptable salt or prodrug thereof.

7. A method according to Claim 6 for the treatment or prevention of pain or inflammation.

15 8. A method according to Claim 6 for the treatment or prevention of migraine.

9. A method according to Claim 6 for the treatment or prevention of emesis.

10 10. The use of a compound as claimed in any one of claims 1 to 3 for the manufacture of a medicament for the treatment of a physiological disorder associated with an excess of tachykinins.

25 11. The use of a compound as claimed in any one of claims 1 to 3 for the manufacture of a medicament for the treatment of pain or inflammation.

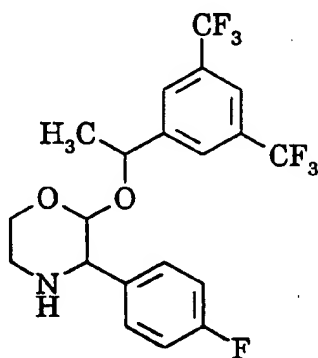
30 12. The use of a compound as claimed in any one of claims 1 to 3 for the manufacture of a medicament for the treatment of migraine.

13. The use of a compound as claimed in any one of claims 1 to 3 for the manufacture of a medicament for the treatment of emesis.

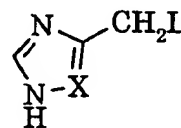
5 14. A process for the preparation of a compound of formula (I) which comprises:

(A) reacting a compound of formula (II) with a compound of formula (III):

10



(II)



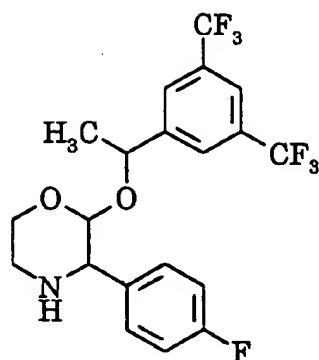
(III)

wherein X is N or CH, and L is a leaving group, or a protected derivative thereof; or

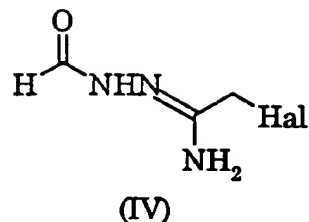
15

(B) wherein X is N, by reacting a compound of formula (II) with a compound of formula (IV):

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(II)



(IV)

wherein Hal is a halogen atom; in the presence of a base;

5 each process being followed, where necessary, by the removal of any protecting group where present;

 and when the compound of formula (I) is obtained as a mixture of enantiomers or diastereoisomers, optionally resolving the mixture to obtain the desired enantiomer;

10 and/or, if desired, converting the resultant compound of formula (I) or a salt thereof into a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 95/00983

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D413/06 A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 577 394 (MERCK & CO. INC.) 5 January 1994 cited in the application see page 18 - page 20; claims 1-4,6,7 ---	1-5, 10-13
P,A	WO,A,94 19323 (MERCK SHARP & DOHME LIMITED) 1 September 1994 see claims 1-10,12,13,19-22 ---	1-5, 10-13
E	WO,A,95 16679 (MERCK & CO., INC.) 22 June 1995 see claims 1-11,16-26 ---	1,4,5, 10-14
E	WO,A,95 18124 (MERCK SHARP & DOHME LIMITED) 6 July 1995 see page 60, description 11 see claims 1,2,5,15-26 -----	1,2,4,5, 10-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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O document referring to an oral disclosure, use, exhibition or other means

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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search

11 August 1995

Date of mailing of the international search report

3. 10. 95

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 95/00983

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		NO-A- 945064	28-02-95
		SI-A- 9300346	31-12-93
		WO-A- 9400440	06-01-94
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WO-A-9518124	06-07-95	NONE	